

Applicants wish to thank Examiner Li, and Supervisor Kunz for their discussion of this case with Applicants' agent on June 4, 2003. The substance of that discussion, and the conclusions reached are incorporated into the following response.

Formal Matters

Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

Previous Amendment

The Examiner notes that Applicant's amendment in Paper No. 8 filed on December 5, 2001 has not been entered because the amendment does not correspond to the specification. Applicants submit that they have re-checked the amendments made on December 5, 2001 and they correspond to the cited pages of Applicant's copy of the specification. Applicant's request additional clarification from the Examiner as to where, specifically, the lack of correspondence occurs.

Rejection of claims 7-14, 24-24, and 26-28 under 35 U.S.C. §101

The Examiner has rejected claims 7-14, 23, 24, and 26-28 under 35 U.S.C. §101 for lack of utility. The Examiner asserts that the invention is not supported by either a well established utility or a specific, substantial, and credible utility. Applicants respectfully disagree.

The Examiner asserts that because the specification does not disclose the precise biological function of GPR86, one of skill in the art would not be able to recognize the specific and substantial use of GPR86, or the claimed methods of screening for candidate modulators of GPR86 activity. The Examiner also asserts that although the specification teaches that the invention provides methods of diagnosing a disease or disorder characterized by dysregulation of GPR86 signaling, the utility is not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. Applicants respectfully submit that the Examiner is in error.

The Utility Examination Guidelines (Fed. Reg. 66, 2001, p. 1092) clearly articulate that if the applicant has asserted that the claimed invention is “useful for **any particular practical purpose** (i.e., it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility”. The guidelines go on to explain the meaning of specific and substantial describing that the requirement excludes “throw away”, “insubstantial” or “nonspecific” utilities, “such as the use of a complex invention as landfill”. The guidelines indicate that credibility is to be judged from the perspective of one of ordinary skill in the art, and that Applicants need only provide one credible assertion of a specific and substantial utility to meet the requirement.

Applicants submit that the GPR86 receptor of the present invention is a receptor for ADP, a molecule which is well established in the art as regulating a number of cellular physiological functions, and as such has a specific, substantial, and credible utility. Applicants submit that the state of the art at the time the application was filed, clearly established a physiological role for ADP. For example, ADP has been shown to regulate norepinephrine levels in cat nictitating membrane (Langer and Pinto, 1976, *J. Pharmacol. Exp. Ther.* 196:687; Exhibit 1); to modulate smooth muscle contraction of guinea-pig vas deferens (Westfall et al., 1978, *Eur. J. Pharmacol.* 50:27; Exhibit 2); inhibit adrenergic neurotransmission in rabbit pulmonary artery and aorta (Husted and Nedergaard, 1981, *Acta Pharmacol. Toxicol.*, 49:334; Exhibit 3); induce platelet aggregation (Ganchev et al., 1990, *Acta Physiol. Pharmacol. Bulg.*, 16:46; Exhibit 4); stimulate mitogenesis of vascular smooth muscle cells (Erlinge et al., 1995, *Eur. J. Pharmacol.* 289:135; Exhibit 5); stimulate phospholipase C and inhibits adenylate cyclase activity in cultured Schwann cells (Berti-Mattera et al., 1996, *Biochem. J.*, 314:555; Exhibit 6); inhibit Ca^{2+} currents in differentiated neuroblastoma/glioma hybrid cells (Filippov and Brown, 1996, *Eur. J. Neurosci.* 8:1149; Exhibit 7); modulate N-type Ca^{2+} currents in superior cervical ganglion neurons (Filippov et al., 2000, *Br. J. Pharmacol.*, 129:1063; Exhibit 8); stimulate pertussis-toxin insensitive IP_3 accumulation in sympathetic neurons (Bofill-Cardona et al., 2000, *Mol. Pharmacol.*, 57:1165; Exhibit 9); and modulate voltage-activated calcium currents in differentiated PC12 cells (Vartian and Boehm, 2001, *Eur. J. Neurosci.*, 13:899; Exhibit 10). Thus, ADP is well established in its role as a transmitter and modulator of cellular physiology, and is thus, itself possesses a specific and substantial utility. Accordingly, this

utility is imputed onto GPR86 as a receptor for ADP. As discussed by telephone with Examiner Li, and Supervisor Kunz, Applicants' showing of an established utility for ADP establishes a corresponding utility for GPR86 as a receptor for ADP.

In addition, Applicants submit that the present specification teaches that GPR86 (also termed P2Y₁₃) is a member of the P2Y family of adenine nucleotide G-protein coupled receptor family (See figure 2, which shows the structural relatedness of GPR86 to other members of the P2Y receptor family). The P2Y receptor family of receptors are well established in the art, and has been shown to mediate a number of pharmacological and physiological responses in multiple cell types. For example, P2Y receptors have been shown to modulate cellular physiology in pancreatic β -cells, human and murine tumor cells, intestinal epithelial cells, lung epithelial cells, kidney epithelial cells, pulmonary vasculature, goblet cells, chondrocytes, urinary sphincter smooth muscle, platelets, gastrointestinal sympathetic neurons, spermatozoa, brain cortical neurons, brain synaptosomes, and cortical astrocytes (Reviewed in Abbracchio and Burnstock, 1994, *Pharmac. Ther.*, 64:445; Exhibit 11). As described on page 57 of the specification the GPR86 receptor shares 48% amino acid homology with the P2Y₁₂ receptor, which corresponds to a platelet derived ADP receptor (page 1). Thus, GPR86 is a member of a receptor family which is known to mediate numerous physiological responses, and as such, has a specific, substantial, and credible utility.

Lastly, the specification teaches that GPR86 has a particular tissular distribution which is consistent with a role for the receptor in transducing physiological processes mediated by ADP. The specification teaches at page 43, lines 18-23 that

GPR86, which is expressed in cells of the lymphocytic lineages, platelets, spleen as well as leukemic cells, can have a role in immune processes, cancer, thrombosis and associated disorders or diseases. The GPR86 expression pattern also includes the brain and further suggests a potential role as an ADP neurotransmitter. **The expression pattern of GPR86 and the knowledge with respect to disorders generally mediated by GPCRs suggests that GPR86 can be involved in disturbances of....**[the specification then provides a list of target diseases and disorders]

The specification teaches further that the "interaction of GPR86 with ADP can be used as the basis of assays for the diagnosis or monitoring of diseases, disorders, or processes involving

GPR86 signaling” (page 44, lines 7-8). Thus, the specification teaches that GPR86 has a characteristic cellular distribution which is indicative of its role in physiological processes which are consistent with the specific cellular distribution taught in the specification.

Applicants submit that GPCRs are well known to those of skill in the art as transmembrane proteins which function to transduce a signal from the outside to the inside of a cell. Applicants submit further, that the use of a protein’s tissue or cellular distribution is widely accepted by those of skill in the art for purposes of making deductions as to the physiological role of the protein, and its possible function in a disease state. It is well known to those of skill in the art that the putative function for a protein is often based solely on its distribution in a particular set of tissues. See, for example, Beaudet et al., 1998, *J Neurobiol.* 36:325 [teaching that expression of pituitary adenylate cyclase in a population of sympathetic preganglionic neurons was indicative of the peptide functioning as a preganglionic sympathetic neurotransmitter].

The Examiner seems to be asserting that the only disclosure which would satisfy the utility requirement would be a full characterization of protein physiology, and a complete description of protein function. This is not what is required by the utility guidelines. The specification teaches that GPR86 is a G-protein coupled receptor; it teaches that the natural ligand of GPR86 is ADP, a known signaling molecule and neurotransmitter; it teaches that the receptor is expressed in lymphocytic cells, platelets, spleen cells, and the brain, imputing a role for GPR86 in diverse physiological processes including immune processes, cancer, thrombosis, and neurotransmission. Applicants submit that this description is a specific and substantial assertion of a credible utility for GPR86. The Examiner points out that, as cited in *Brenner v. Manson*, 383 U.S. 519 (Sup. Ct. 1966), “a patent is not a hunting license...it is not a reward for the search, but compensation for its successful conclusion”. Applicants concur with this sentiment, however, submit that the present disclosure goes far beyond providing a mere hunting license. Applicants have discovered that ADP, a known signaling molecule, is the natural ligand for the G-protein coupled receptor GPR86, and that the receptor is distributed in specific tissues which is indicative of the receptor, and more importantly, the receptor/ligand interaction having a specific physiological role. In view of the specific and substantial disclosure provided in the

specification, the Examiner has not provided a rationale as to why one of skill in the art would not find such an asserted use to be credible. Applicants submit that given the teachings in the specification, one of skill in the art would readily appreciate and concur with the asserted usefulness of the present invention.

Applicants accordingly submit that the present invention is supported by a substantial, specific, and credible utility, and therefore request that the rejection be reconsidered and withdrawn.

Rejection of claims 7-14, 23, 24, and 26-28 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 7-14, 23, 24, and 26-28 under 35 U.S.C. §112, second paragraph as being indefinite on several grounds.

The Examiner asserts that the claims are indefinite because they recite the term GPR86; the Examiner asserts that GPR86 should be set forth by its SEQ ID NO. Applicants respectfully disagree.

Applicants submit that by their amendment of December 5, 2001, the amino acid sequence of GPR86 was indicated to be set forth in SEQ ID NO: 2. Applicants have further amended the specification herein, to indicate that GPR86 is represented by the nucleic acid sequence of SEQ ID NO: 1 and the amino acid sequence of SEQ ID NO: 2. While the rules governing the disclosure of sequences in a patent application require that “where the description or claim of a patent application **discuss a sequence** that is set forth in the “Sequence Listing”...reference must be made to the sequence by use of the sequence identifier” (37 C.F.R. §1.821), there is no requirement that the mere use of the **name** of a sequence must be accompanied by reference to the sequence identifier. To extend the requirement of 37 C.F.R. 1.821 to the extent suggested by the Examiner would mean that each time GPR86 is mentioned in the specification, Applicants would be required to indicate a sequence identifier; clearly, Applicants are not required to do this. The claims of the present invention refer to GPR86. Given the teaching in the specification and figures, one of skill in the art would readily be able to determine the metes and bounds of GPR86.

Applicants submit that the Examiner has not presented any rationale as to why applicants should be required to modify the claims of the present invention, when they are clear and definite as written. If the Examiner contends that one of skill in the art would be confused by, or not comprehend the scope of the recitation of GPR86 in the claims, given the teachings in the specification, Applicants respectfully request that the Examiner provide Applicants with a rationale to support this position.

The Examiner has rejected claims 7-14 and 26-28 as being indefinite in the recitation of "said second messenger assays" because there is no antecedent basis. The Examiner has rejected the claims further for the recitation of "detecting a signaling activity", because it is unclear what signaling activity is to be determined.

With respect to "said second messenger assays", Applicants submit that they have amended the claims to include proper antecedent basis. With respect to the phrase "detecting a signaling activity", Applicants submit that the specification clearly indicates that "the step of measuring a signaling activity of the GPR86 polypeptide comprises detecting a change in the level of a second messenger" (page 5, lines 24-25). Thus, Applicants submit that, from a reading of the specification, it would be clear to one of skill in the art what is meant by "detecting a signaling activity". Nevertheless, in order to advance prosecution, Applicants have amended the claims herein to recite "detecting a signaling activity of GPR86 polypeptide...*by a second messenger assay*". A "second messenger assay" is defined on page 13 of the specification. Particularly, a "second messenger assay" comprises "the measurement of guanine nucleotide binding or exchange, adenylate cyclase, intra-cellular cAMP, intracellular inositol phosphate, intra-cellular diacylglycerol concentration, arachinoid acid concentration, MAP kinase(s) or tyrosine kinase(s), protein kinase C activity, or reporter gene expression or an aequorin-based assay".

The Examiner has rejected claims 8 and 12 as being indefinite in the recitation of "other cell lines". Applicants submit that the phrase "other cell lines" has been deleted from these claims.

The Examiner has rejected claims 7, 9, 11, 13, and 23 as being indefinite for failing to recite a correlation step linking the detection/selection steps to the goal recited in the preamble. Applicants submit that the claims have been amended to recite an appropriate correlation step.

Applicants submit that the claims are definite as amended, and therefore request that the rejections be reconsidered and withdrawn.

Conclusion

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

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Respectfully submitted,



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MARKED-UP VERSION OF AMENDMENTS:

In the Specification

The present invention is related to the GPR86 (P2Y₁₃) receptor [(identified herein after as SEQ ID NO. 1] (or any homologous sequence), the nucleic acid sequence of which is set forth in SEQ ID NO: 1 and the amino acid sequence of which is set forth in SEQ ID NO: 2 and a recombinant cell (transformed by a suitable vector) comprising the nucleotide sequence encoding the receptor, as well as the natural ligands (ADP and equivalent molecules such as 2MeSADP, ADP β S including any of the ADP analogues presented in US PAT. NO 5,700,786) to be used in screening assays for identification of agonists, inverse agonists or antagonist compounds useful for the development of new drugs and the improvement of various disease diagnostics.

In the Claims

7. (Amended) A method of screening for a candidate modulator of GPR86 activity using cells expressing GPR86, said method comprising:

a) incubating a first sample of said cells in the presence of said candidate modulator and a second sample of said cells in the absence of said candidate modulator, both said samples under conditions which permit binding of ADP to GPR86;

b) detecting a signalling activity of GPR86 polypeptide in said first and second samples by a second messenger assay, and

c) comparing the results of said second messenger assays for said first and second samples, wherein a difference in activity between said first and second samples is indicative of said candidate modulator being a modulator of GPR86 activity.

8. (Amended) The method of claim 7 wherein said cell is selected from the group consisting of: COS7-cells, a CHO cell, a LM (TK-) cell, a NIH-3T3 cell, HEK-293 cell, K-562 cell, a 1321N1 astrocytoma cell [and other cell lines].

9. (Amended) A method of screening for a candidate modulator of GPR86 activity using cell membranes bearing GPR86, said method comprising:

a) incubating a first sample of said cell membranes in the presence of said candidate modulator and a second sample of said cell membranes in the absence of said candidate modulator, both said samples under conditions which permit binding of ADP to GPR86;

b) detecting a signalling activity of GPR86 polypeptide in said first and second samples by a second messenger assay, and

c) comparing the results of said second messenger assays for said first and second samples, wherein a difference in activity between said first and second samples is indicative of said candidate modulator being a modulator of GPR86 activity.

11. (Amended) A method for determining if a candidate modulator increases or decreases the activity of GPR86 using cells expressing GPR86, said method comprising:

a) incubating a first sample of said cells in the presence of said candidate modulator and a second sample of said cells in the absence of said candidate modulator, both said samples under conditions which permit binding of ADP to GPR86;

b) detecting a signalling activity of GPR86 polypeptide in said first and second samples by a second messenger assay, and

c) comparing the results of said second messenger assays for said first and second samples, wherein a difference in activity between said first and second samples is indicative of said candidate modulator as increasing or decreasing GPR86 activity.

12. (Amended) The method of claim 11 wherein said cells are selected from the group consisting of: COS7-cells, a CHO cell, a LM (TK-) cell, a NIH-3T3 cell, HEK-293 cell, K-562 cell and a 1321N1 astrocytoma cell [and other cell lines].

13. (Amended) A method for determining if a candidate modulator increases or decreases the activity of GPR86 using cell membranes bearing GPR86, said method comprising:

a) incubating a first sample of said cell membranes in the presence of said candidate modulator and a second sample of said cell membranes in the absence of said candidate modulator, both said samples under conditions which permit binding of ADP to GPR86;

b) detecting a signalling activity of GPR86 polypeptide in said first and second samples by a second messenger assay, and

c) comparing the results of said second messenger assays for said first and second samples, wherein a difference in activity between said first and second samples is indicative of said candidate modulator increasing or decreasing GPR86 activity.

23. (Amended) A method of identifying an agent that modulates the function of GPR86, said method comprising:

a) contacting a GPR86 polypeptide in the presence and absence of a candidate modulator under conditions permitting the binding of said ADP to said GPR86 polypeptide; and

b) measuring the binding of said GPR86 polypeptide to said candidate modulator, relative to the binding in the absence of said candidate modulator, wherein a difference in binding identifies said candidate modulator as an agent that modulates the function of GPR86.